Remarks

Claims 13, 15-17, 19-21 and 23-24 are pending. Claims 14-15, 18-19, 22 and 24 are cancelled. Claims 13, 16, 17, 20, 21 and 23 are currently amended. Support for the amendments can be found at, for example, paragraphs [0052], [0071] and [0072] in the originally filed application and the previous version of Claim 13. Additional support for the amendments can also be found at, for example, paragraphs [0034], [0036], [0039], [0041], [0052], [0060], [0062], [0088], [0095], [0102], [0120] and [0134] of the originally filed application. The Applicants also note the amendment of the claims to recite that the site of administration is intramuscular or intratumoral is consistent with the discussion during the interview. Claims 13, 15-17, 19-21 and 23-24 are rejected. The objections and rejections with regard to Claims 14-15, 18-19, 22 and 24 are now moot as these claims have been cancelled.

The Applicants wish to thank the Examiner for the helpful interview of December 8, 2008 in which the claim objections as well as the rejections made under 35 USC §112, first paragraph and 35 USC §103(a) were discussed. The amendments and the arguments here are consistent with the discussion during the interview and the Examiner's helpful guidance.

Additionally, the Applicants note with appreciation the Examiner's acknowledgement during the interview that one of ordinary skill in the art would recognize that in the methods of the disclosure the recombinant expression of a nucleic acid encoded protein domain, such as a disintegrin domain, from an expression plasmid *in vivo* necessarily results in the expression of different post-translationally modified forms of the protein domain disintegrin domain in the methods of the disclosure (*e.g.* Ala-2 to Glu-91 of SEQ ID NO: 2 produced by deformylase or methionine aminopeptidase activity, glycosylated forms, phosphorylated forms, disulphide bonds *etc.* resulting from post-translational modification).

The Official Action states that Claims 15, 16, 19, 20, 23 and 24 will be objected to if certain of these claims are allowed. The Applicants have cancelled Claims 15, 19 and 24 in anticipation of the allowance of amended Claims 16, 20 and 23. The Applicants respectfully request that the objections to the claims be withdrawn.

Claims 13, 16, 17, 20, 21 and 23 have been rejected under 35 USC §112, first paragraph, as being non-enabled.

Amended Claims 13, 16, 17, 20, 21 and 23 are enabled under 35 USC §112, first paragraph. Independent Claims 13, 17 and 21 have been amended to recite administering by "electrotransfer to an intramuscular site or an intratumoral site in the mammal a therapeutically effective amount of an expression plasmid coding for the disintegrin domain encoded by a polynucleotide consisting of the polynucleotide shown in SEQ ID NO: 1 where SEQ ID NO: 1 is operably linked to a promoter or expression control sequence." The remaining claims are dependent on these independent claims and include all of their recitations.

The amended claims now specify that the nucleic acid administered "is operably linked to a promoter or expression control sequence" and thus has the ability to express the disintegrin encoded by the polynucleotide shown in SEQ ID NO: 1. The Applicants also note that this amendment is consistent with the Examiner's very helpful suggestion during the interview. Importantly, expression plasmids suitable for expression of polypeptides encoded by a polynucleotide, such as the pBi vector used in the examples of the application, and many other such expression plasmids are well known in the art. Such expression plasmids can be easily constructed and used for the expression of peptide chains, such as protein domains, by one of ordinary skill in the art without undue experimentation.

The amended claims now also specify that the expression plasmid is administered to the mammal by "electrotransfer to an intramuscular site or an intratumoral site[.]" Electrotransfer techniques and equipment for delivery of nucleic acids molecules such as expression plasmids to mammal and other animals are well known in the art. One example of such equipment is the commercially available electropulsator PS-15 manufactured by Jouan (St. Herblain, France). Another example is the commercially available CLINIPORATOR™ manufactured by iClin Solutions (Malmo, Sweden; *see also* www.iclin.se/products.html). One of ordinary skill in the art is clearly capable of using such electrotransfer equipment and related techniques for the delivery of expression plasmids without undue experimentation.

The application also includes numerous working examples providing detailed guidance sufficient to permit one of ordinary skill in the art to perform the claimed methods without undue experimentation. Importantly, these examples are performed in several different art accepted models of tumor metastases, angiogenesis, and melanoma mediated disease including both animal based *in vivo* models and *in vitro* models of these processes. *See e.g.* Figs. 1-10 and

Examples. Thus, one of ordinary skill in the art is clearly enabled to perform the claimed methods without undue experimentation.

The Applicants also submit a Declaration under 37 CFR §1.132 by Dr. Véronique Trochon-Joseph containing evidence which demonstrates the claimed methods can be performed by one of ordinary skill in the art without undue experimentation. *See* enclosed Declaration of Véronique Trochon-Joseph made under 37 CFR §1.132. These data show that a variety of different expression plasmids can be used to express the disintegrin domain encoded by a polynucleotide consisting of the polynucleotide shown in SEQ ID NO: 1. These expression plasmids include the commercially available pVAX and pORT vectors as well as the pBi vector discussed above. The data also show that electrotransfer consistently works in a variety of different models and that electrotransfer can be used to directly deliver expression plasmids to muscle (*i.e.* intramuscularly) or tumors (*i.e.* intratumorally) present in mammals. Importantly, the data also consistently show that anti-tumor effects can be achieved with the claimed methods in these different models. In other words, these data clearly show that the claimed methods can be performed by one of ordinary skill in the art without undue experimentation.

Additionally, as the discussion above makes clear, the scope of the amended claims has now been limited. This means the claims no longer recite the use of a broad group of means to perform the methods of the invention. Stated differently, the scope of the amended claims is consistent with the scope of enablement provided by the application and the knowledge in the art such that undue experimentation is not required to practice the claimed methods.

The Applicants respectfully request the withdrawal of the rejections of Claims 13, 16, 17, 20, 21 and 23.

Claims 13, 16, 17 and 20 have been rejected as obvious under 35 USC §103(a) over the combination of US '609, US '465 and US '368.

Amended Claims 13, 16, 17 and 20 are not obvious under 35 USC §103(a) over the combination of US '609, US '465 and US '368. Reasons are set forth below.

First, the combination of US '609, US '465 and US '368 fails to teach all the elements of the claimed methods. This is because none of these references teach the direct administration to a mammal by electrotransfer of an expression plasmid coding for the specific disintegrin domain encoded by a polynucleotide consisting of SEQ ID NO: 1. US '609, for example, merely

describes a method in which the contortrostatin protein is injected directly. US '465 and US '368 similarly fail to teach all the elements of the amended claims.

US '368, in particular, fails to describe the use of the disintegrin domain of SEQ ID NO: 2 alone or an anti-metastatic or anti-angiogenic activity biological activity for this domain by itself. Additionally, SEQ ID NO: 4 in US '368 comprises a total of 814 amino acid residues while US '368 provides absolutely no guidance concerning which portions of this protein will have anti-metastatic or anti-angiogenic activity. Most importantly, this means the use of the nucleic acid of SEQ ID NO: 1 alone in the claimed methods cannot be obvious over US '609, US '465 and US '368 because the cited references fail to teach all the elements of the claimed methods. In fact, as discussed with the Examiner during the interview, this is why the claims were amended to include the "consisting of" language. Consequently, the amended claims cannot be obvious over the combination of US '609, US '465 and US '368.

Second, US '368 merely discloses that the amino acid sequences of metalloprotease proteins have a protease activity. In contrast, the claimed methods relate to the use of the disintegrin domain of SEQ ID NO: 1 which has an anti-angiogenic activity (*i.e.* inhibits the migration and proliferation of endothelial cells, and induces the apoptosis of endothelial cells). *See e.g.* paragraph [0017] of the originally filed application. Importantly, this anti-angiogenic activity is apparently unrelated to any protease activity. This means that US '368 does not teach the administration of the disintegrin domain of SEQ ID NO: 1 for decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases. Stated differently, the claimed methods cannot be obvious over US '368 because this reference fails to teach all the elements of the claimed methods and one of ordinary skill in the art would not be motivated to combine US '368 with the other cited references.

Third, one of ordinary skill in the art would not be motivated to combine the teachings of US '609 and US '465 with US '368. This is because US '609 merely describes a specific disintegrin, named contortrostatin, that apparently has an anti-metastasic activity. However, contortrostatin is a totally different protein, in terms of its amino acid sequence, than the disintegrin domain used in the method of the invention.

This is important because the activity of the disintegrin domain encoded by SEQ ID NO: 1 cannot simply be deduced from the teachings of US '609. Indeed, as the Examiner correctly

notes the ADAMS subfamily includes multiple proteins that have the potential to treat a myriad of conditions. However, these conditions cannot automatically be known or otherwise immediately identified for each specific member of the subfamily. This is especially true when only a fragment of such a subfamily member is expressed alone. Stated differently, one of ordinary skill in the art would not be motivated to use the disintegrin domain encoded by the polynucleotide consisting of SEQ ID NO: 1 to decrease intratumoral vessels to inhibit growth of melanoma and pulmonary metastases in a mammal without knowledge of the specific biological functions of this unique disintegrin domain. Importantly, such knowledge is not provided by any of the cited references.

Furthermore, the contortrostatin described in US '609 is isolated from snake venom. However, as noted in the specification of this application, AMEP such as SEQ ID NO: 1 are distinct from snake disintegrins for at least two reasons. One reason is that snake disintegrins exert only a limited effect on different stages of angiogenesis while AMEP inhibits all stages of angiogenesis. Another reason is that AMEP has a human origin and thus does not have the highly antigenic character of the snake disintegrins which makes snake disintegrins unsuitable for use as drugs in the long-term therapy required in anticancer treatment. Altogether, this means that one of ordinary skill in the art would not be motivated to combine the teachings of US '609 with the other cited references and would not reasonably expect success in so doing.

Fourth, US '465 teaches novel ADAM polypeptides, but it does not teach the disintegrin domain of SEQ ID NO: 1 nor its use alone in the method of the invention. For the same reasons set forth above with regard to US '609, it is not possible from the disclosure of US '465 to know that the unique disintegrin domain used in the methods of the claims could decrease intratumoral vessels to inhibit growth of melanoma and pulmonary metastases.

Fifth, Nath clearly teaches away from the expression and use of the disintegrin domain of metargidin (SEQ ID NO: 1) alone. *See* Nath *et al.*, 112 J. Cell Sci. 579 (1999) (courtesy copy attached). This is because Nath teaches that "the disintegrin domain of metargidin alone may not be stable on its own, due to the presence of an odd number of cysteine residues, which may be part of an inter-domain disulphide bond or may be involved in receptor oligomerisation." *See* Nath at 581, column 2. Nath also teaches that expression of the metargidin disintegrin domain alone results in a loss of biological activity such as $\alpha 5\beta 1$ integrin binding. *See* Nath at 585,

column 2. This means that one of ordinary skill in the art would not be motivated to combine and modify the teachings of US '609, US '465 and US '368 as suggested in the rejection because Nath teaches away from so doing. The Applicants respectfully request that the Examiner consider all the teachings of the prior art including those, as in Nath, which teach away from the claimed methods.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/vbm
(215) 656-3381